REMARKS

Applicant expresses appreciation to the Examiner for consideration of the subject patent application. Claims 1-79 are pending. Claims 45-79 have been withdrawn. Claims 1 and 21-25 have been amended.

Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the Office Action of January 20, 2011, the following actions were taken:

(1) Claims 1-24, 26-27, and 31-44 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over "Nickel-Dependent Oxidative Cross-Linking of a Protein" by Gill et al., *Chem. Res. Toxicol.*, 10(3), 302-309 (1997) (hereinafter "Gill"); and

(2) Claim 1-24, 26-29, and 31-44 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,087,452 (hereinafter "Stewart") in view of "A Critical Role for Tyrosine Residues in His6Ni-Mediated Protein Cross-Linking" by Fancy et al., *Biochem. Biophys. Res. Comm.*, 247, 420-426 (1998) (hereinafter "Fancy").

It is respectfully submitted that the presently pending claims be allowed in view of the telephone interviews held and based on the remarks below.

Claim Amendments

The Applicant has amended claim 1 as suggested by the Examiner and as supported throughout the specification including paragraph [0010-0014] and claims 21-25. In light of the above amendment, claims 2, 8, and 11 were amended to correct antecedent basis. Additionally, claim 5 was amended to correct a typographical error. In light of the present amendment to claim 1, claims 22-25 and 15-19 were canceled. As such, the Applicant submits that no new matter has been added.

Specification Amendments

The specification was amended to include the subject matter of originally filed claims 21-25. As such, the Applicant submits that no new matter has been added.

Claim 30

The Applicant notes that claim 30 has been identified by the Examiner as nonelected. However, the Applicant has elected Group I (claims 1-44) and species (A), (B), (C, D), (E), and (G). The Applicant notes that claim 30 was identified by the Examiner as pertaining to Group I and specifically to species (E). Office Action dated 8/31/10, page 2 and 3. As such, the Applicant submits that claim 30 has been elected for prosecution in accordance with Applicant's election. The Applicant submits that any prior omission of claim 30 on Applicant's part was inadvertent and requests consideration of claim 30 in the current prosecution.

Claim Rejections - 35 U.S.C. § 103

Before discussing the obviousness rejections herein, it is thought proper to briefly state what is required to sustain such a rejection. The issue under § 103 is whether the PTO has stated a case of *prima facie* obviousness. The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner that a *prima facie* case of obviousness generally includes establishing 1) that the asserted references as modified or combined teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined provide a sufficient likelihood of successfully making the modification or combination, and 3) a reason for the modification or combination asserted.

Additionally, under *KSR*, and as outlined under the MPEP § 2143, additional rationales include (a) combining prior art elements according to known methods to yield predictable results; (b) simple substitution of one known element for another to obtain predictable results; (c) use of known technique to improve similar devices (methods, or products) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (e) "obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and (g) some teaching, suggestion, or motivation in the prior art that would have led

one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Claim 1-24, 26-27, and 31-44 over Gill

The Examiner has rejected claim 1-24, 26-27, and 31-44 over Gill. Specifically, the Examiner alleges that Gill teaches the present elements of independent claim 1. The Applicant traverses the present rejection.

The Examiner alleges that Gill teaches phenolic metal ligands added to the first and second moieties and that such ligands are subsequently cross-linked. However, the Applicant respectfully disagrees. First, the Applicant notes that the present claims require 4 distinct steps: attaching a first metal ligand to a first moiety; attaching a second metal ligand to a second moiety, add a metal ion to form a coordinate complex between the first moiety and the second moiety, cross-linking the first and second moieties by exposing the coordination complex to an oxidizing agent to form a covalent crosslink between the phenolic groups or the phenolic derivatives. As such, the Applicant notes that the present method forms a coordination complex independently of the cross-linking of the phenolic or phenolic derivative groups. The Applicant submits that Gill does not teach each of the present steps.

Specifically, the Applicant submits that Gill does not teach attaching a first metal ligand to a first moiety or attaching a second metal ligand to a second moiety. Notably, Gill only discloses intermolecular coupling of RNases. In other words, Gill is taking existing compounds and crosslinking such compounds. Gill fails to disclose any step of adding first or second metal ligand to its RNases.

The Applicant acknowledges that Gill discloses coupling of RNases using "accessible tyrosines on the surface of RNase." Page 305, left column, bottom paragraph. However, the Applicant submits that such disclosure distinguishes the present method that specifically requires attachment of metal ligands before complexation and cross-linking.

Further, the Applicant notes that the mechanism provided in Gill is distinct from the present method. Specifically, Scheme 1 on page 307 shows a Ni ion coordinates the amide groups of consecutive amino acid groups within a singe RNase compound allowing intramolecular electron transfer and subsequent intermolecular cross-linking. However, the Applicant notes that the present claims require "adding a metal ion to form a coordination complex between the first moiety and the second moiety." The Applicant submits that the metal

ion disclosed in Gill does not form a coordinate complex between a first and second moiety but forms a coordinate complex within a single moiety; i.e., the RNase as shown in Scheme 1.

More importantly, the Applicant has amended the present claims to include that the second moiety comprises fluorescein, the subject matter of former claim 25. Notably, claim 25 was not rejected by the present reference. As such, the Applicant submits that, in addition to the above arguments, the present claims now contain an element not disclosed by Gill.

In light of the above, the Applicant submits that Gill does not teach each and every element of claims 1-24, 26-27, and 31-44. As such, the Applicant respectfully requests that the Examiner withdraw the present rejection.

Claims 1-24, 26-29, and 31-44 over Stewart in view of Fancy

The Examiner has rejected claim 1-24, 26-29, and 31-44 over Stewart in view of Fancy. Specifically, the Examiner alleges that Stewart teaches the present elements of independent claim 1 but acknowledges that Stewart does not teach cross-linking phenolic or phenolic derivative groups. As such, the Examiner cites to Fancy as allegedly teaching cross-linking of HY-tags. The Applicant traverses the present rejection.

The Applicant notes that Stewart discloses similar subject matter as Ho (in fact each of the present inventors are listed on the Ho reference). For example, Figure 1 of Ho corresponds to Figure 1 of Stewart. As such, the Applicant submits that the comments with respect to Ho, as discussed above, are equally applicable in the present rejection. To be clear, the Applicant submits that Stewart teaches a coordination complex between NTA-modified PEO blocks (of Pluronic F108) with a metal and histidine-tagged proteins. FIG. 1; col. 3, lines 46-54; col. 7, lines 9-43. The coordination complex is shown in detail in Figure 1 of Stewart and involves nitrilotriacetic acid groups, a metal ion, and two imidazole groups of the histidine tag on the protein. In other words, Stewart does not teach a phenolic group or phenolic derivative of a first moiety that is cross-linked with a phenolic group or phenolic derivative of a second moiety. Rather, Stewart teaches coordination between imidazole groups, a metal ion, and nitrilotriacetic acid groups.

The Examiner has acknowledged that Stewart does not teach cross-linking phenolic groups but cites to Fancy for such a teaching. However, Stewart specifically utilizes coordination rather than covalent cross-linking since one of Stewart's objectives is to have "reversible binding under non-denaturing conditions." Col. 2, lines 28-32. As such, the

Applicant submits that utilizing cross-linking would destroy this explicit functionality as stated in Stewart. In other words, the Applicant submits that Stewart teaches away from the cross-linking presently claimed.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a **direction divergent** from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Clearly in the present case, a person of ordinary skill in the art would be led in a path divergent from that taken by Applicant since Stewart specifically uses coordination, which is reversible, while the present invention provides for covalently bonding through cross-linking.

More importantly, the Applicant has amended the present claims to include that the second moiety comprises fluorescein, the subject matter of former claim 25. Notably, claim 25 was not rejected by the present combination. As such, the Applicant submits that, in addition to the above arguments, the present claims now contain an element not disclosed by the combination of Stewart and Fancy.

Regarding Fancy, the Applicant acknowledges that during the telephone interviews between Applicant and Examiner Weber and Examiner Kosar, it was suggested that Fancy may anticipate claim 1. However, the Applicant has included amendments to claim 1 including that the second moiety comprises fluorescein. The Applicant notes that Fancy does not disclose,

fluorescein or labeling of proteins; rather, Fancy only discloses cross-linking to form "multiprotein complexes." Abstract. As such, the Applicant notes that Fancy does not teach each and every element of the pending claims.

In light of the above, the Applicant submits that the Stewart and Fancy, alone or in combination, do not teach each and every element of the pending claims. Further, the Applicant notes that Stewart teaches away from the present invention as well as Fancy. As such, the Applicant respectfully requests that the Examiner withdraw the present rejection.

CONCLUSION

In light of the above, Applicant respectfully submits that claims 1-14, 20-21, and 26-44 are in condition for allowance. Therefore, Applicant requests that the rejections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after consideration of the above amendments and remarks, the Examiner is encouraged to call the undersigned at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 21st day of November, 2011.

Respectfully submitted,

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